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Description

According to the present invention there is provided the use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride for the manufacture of a medicament for the treatment of obesity, in which treatment the compound is administered in conjunction with a pharmaceutically acceptable diluent or carrier.

The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of depression is described in British Patent Specification 2098602 and the use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. A particularly preferred form of this compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride) which is described in European Patent Application 230742.

The therapeutically active compound may be administered in any of the known pharmaceutical dosage forms for example solid dosage forms such as tablets or capsules or liquid dosage forms for example those forms intended for oral or parenteral administration. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses.

The ability of sibutramine hydrochloride to cause weight reduction in humans has been demonstrated by the following trials.

Trial 1

39 male healthy volunteer subjects were treated in 3 groups. A first group (Group 1) of 15 subjects were given 2.5 mg sibutramine hydrochloride per day for the first two weeks of the trial, followed by 5 mg sibutramine hydrochloride per day for the remaining four weeks of the trial. The second group (Group 2) of 15 subjects were given 5 mg sibutramine hydrochloride per day for the first two weeks of the trial, followed by 10 mg sibutramine hydrochloride per day for the remaining four weeks of the trial. The third group (Group 3) of 9 subjects were given a placebo containing no sibutramine hydrochloride. The subjects were treated with a single dose of sibutramine hydrochloride or placebo taken each morning of the trial. The weight of each subject was taken at the commencement of treatment and after six weeks. The weight of each subject (in kg) at the start and the change in weight (in kg) over the six week trial period is given in Table 1 below.

TABLE 1

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Group 1 given 2.5-5 mg

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weight at startweight change

15

71.4

-3.2

90.5

-4.1

74.1

-2.3

71.4

-2.3

102.7

-7.2

20

74.5

-2.9

78.2

-4.6

84.1

0

63.6

-0.2

25

81.4

-2.3

73.6

-3.6

87.7

-2.2

30

70.0

-4.1

105.9

+0.5

85.0

-0.9

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mean

80.94 \pm 11.99-2.63 \pm 2.01

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TABLE 1 (cont)

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Group 2 given 5-10 mg

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weight at startweight change

15

76.4

-3.9

83.6

-1.8

73.2

-1.4

67.3

-2.3

79.1

0

20

78.0

-2.2

83.6

-6.3

76.8

-5.7

69.5

-1.3

25

71.8

-3.6

82.7

-5.0

75.0

-1.4

30

75.9

-3.2

89.8

-3.4

68.2

-1.8

35

mean

76.73 \pm 6.34-2.89 \pm 1.78

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50

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TABLE 1 (cont)

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Group 3 given placebo

	<u>weight at start</u>	<u>weight change</u>
10		
	78.1	-1.1
	75.9	-0.4
15	77.3	-0.3
	76.4	-1.9
	81.8	-0.7
20	60.2	+3.0
	67.3	-2.1
	65.0	-1.8
	73.6	+3.7
25		
	mean	
	72.84 ± 7.09	-0.18 ± 2.11

Trial 2

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56 subjects who had been diagnosed as suffering from depression were treated in two groups. A first group (Group 1) of 26 subjects were treated with 10 mg of sibutramine hydrochloride per day for the first two weeks of the trial and then with 20 mg of sibutramine hydrochloride per day for a further period of four weeks. The second group (Group 2) were given a placebo containing no sibutramine hydrochloride every day throughout the trial. The subjects were treated with a single dose of sibutramine hydrochloride or placebo taken each morning of the trial. The weight of each subject was taken at the commencement of the trial and after six weeks. The weight of each subject (in kg) at the start and the change in weight (in kg) over the six week period are given below in Table 2.

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TABLE 2

5	<u>Group 1</u>	<u>weight at start</u>	<u>weight change</u>
10		53.6	-1.1
		59.5	-1.6
		81.3	+1.4
15		84	-3.1
		57.3	-0.3
		78.2	-2.3
		86.4	-5.0
20		78.0	-5.3
		89.8	-0.8
		93.5	-0.6
25		64.5	-0.4
		71.8	-5.0
		81.8	+3.2
		84.5	-2.2
30		103.2	-3.2
		55.5	-1.9
		80.9	-1.4
35		67.0	-1.3
		87.2	-4.8
		92.9	0
40		96.5	-0.9
		60.2	-2.2
		68.9	-0.9
		84.7	0.5
45		94.7	-1.8
		93.3	-0.7
50	mean	78.4 ± 13.2	-1.6 ± 2.0

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TABLE 2 (Cont)

5	<u>Group 2</u>	<u>weight at start</u>	<u>weight change</u>
10		79.5	+0.5
		84.4	+1.5
		85.0	-1.6
		89.7	+2.1
15		58.2	-5.4
		79.5	-0.9
		79.5	0
20		97.5	+6.1
		66.7	+0.4
		59.5	-0.4
		68.6	+1.9
25		70.9	+0.9
		88.6	+3.2
		89.1	+1.3
30		67.7	-0.4
		78.2	-1.8
		65.5	+0.4
		68.1	+2.1
35		74.8	+1.8
		86.4	+0.8
		88.0	-0.6
40		99.2	+1.9
		102.4	+1.3
		68.9	-0.5
45		78.8	0
		79.3	+2.2
		85.6	+0.9
		97.4	-1.6
50		46.2	-0.5
		70.2	+0.5
55	mean	78.4 ± 13.2	+0.5 ± 2.0

Trial 3

19 male healthy volunteers were treated in 2 groups. A first group (Group 1) of 14 subjects were treated with 15 mg of sibutramine hydrochloride per day for the first two weeks of the trial and then with 30 mg of sibutramine hydrochloride for a further period of four weeks. The second group (Group 2) were given a placebo containing no sibutramine hydrochloride every day throughout the trial. The subjects were treated with a single dose of sibutramine hydrochloride or placebo taken each morning of the trial. The weight of each subject was taken at the commencement of the trial and after six weeks. The weight of each subject (in kg) at the start of the trial and the change in weight (in kg) over the six week period are given below in Table 3.

TABLE 3Group 1

<u>weight at start</u>	<u>weight change</u>
67.0	-5.4
76.6	-5.5
91.1	-5.5
76.7	-4.7
85.6	-1.3
75.2	-6.8
83.2	-5.5
74.3	-0.9
84.3	-5.9
81.1	0
80.2	-6.8
83.4	-7.0

TABLE 3 (Cont.)

5	<u>Group 1</u>		
		<u>weight at start</u>	<u>weight change</u>
10		77.5	-1.4
		87.4	-4.9
15	mean	80.3	-4.4 ± 2.4 kg
	<u>Group 2</u>		
20		84.5	-0.2
		89.7	1.6
		74.3	-0.5
25		68.5	2.2
		78.6	0.2
30	mean	79.1	$+0.7 \pm 1.2$

From the results reported above for Trials 1, 2 and 3 it can be seen that the subjects treated with sibutramine hydrochloride experienced a significant loss of weight over the six week period of each trial when compared to subjects treated with placebo.

Claims

1. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the manufacture of a medicament for the treatment of obesity.
2. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate in the manufacture of a medicament for the treatment of obesity.

Patentansprüche

1. Verwendung von N,N-Dimethyl-1-[1-(4-chlorphenyl)cyclobutyl]-3-methylbutylamin-Hydrochlorid zur Herstellung eines Medikaments zur Behandlung von Fettleibigkeit (Obesitas).
2. Verwendung von N,N-Dimethyl-1-[1-(4-chlorphenyl)cyclobutyl]-3-methylbutylamin-Hydrochloridmonohydrat zur Herstellung eines Medikaments für die Behandlung von Fettleibigkeit.

Revendications

1. Utilisation du chlorhydrate de N,N-diméthyl-1-[1-(4-chlorophényl)cyclobutyl]-3-méthylbutylamine dans la préparation d'un médicament destiné au traitement de l'obésité.

2. Utilisation du chlorhydrate de N,N-diméthyl-1-[1-(4-chlorophénylcyclobutyl)-3-méthylbutylamine mono-hydraté dans la préparation d'un médicament destiné au traitement de l'obésité.

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